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Predicting response: noradrenaline reuptake inhibition

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For the past decade, the role of noradrenaline in depression has been somewhat neglected in favour of serotonin. This is largely because of the advent of the selective serotonin reuptake inhibitors, which have facilitated clinical and experimental observation of the roles of serotonin. Until now, no such tools have been available to study the noradrenergic system. However, the recent development of reboxetine, the first selective noradrenaline reuptake inhibitor, has allowed clinical investigation of the role of the noradrenergic system in different aspects of depressive disorders. In clinical trials, the use of reboxetine has shown that selective noradrenaline reuptake inhibition is an effective approach to alleviating depression. It is more effective than placebo and at least as effective as desipramine, imipramine and fluoxetine in the short term. In addition, its efficacy is maintained in patients with severe depression and in those receiving long-term maintenance treatment. Reboxetine is very well tolerated, as predicted from its pharmacological profile, having fewer anticholinergic side-effects than imipramine or desipramine. Compared with fluoxetine, patients treated with reboxetine experienced less nausea and sexual dysfunction, adverse events that are common among those taking selective serotonin reuptake inhibitors. Adverse events predicted by the neuroanatomy of the noradrenergic system, such as tremor and cardiovascular effects, occurred less frequently than expected. Clinical experience with reboxetine challenges our current knowledge of the role of noradrenaline in depression and questions existing evidence based on studies with noradrenergic tricyclic antidepressants. Selective noradrenaline reuptake inhibition, as exemplified by reboxetine, therefore offers a significant improvement in antidepressant pharmacotherapy, and an opportunity to increase our understanding of the role of noradrenaline in depression. Int Clin Psychopharmacol 14 (suppl 1):S21–S26 © 1999 Lippincott Williams & Wilkins

Keywords: selective noradrenaline reuptake inhibition, depression, anxiety, reboxetine

INTRODUCTION

At present, our understanding of the role of noradrenaline in depression is less clear than our understanding of the role of serotonin. This is the result, at least partially, of the fact that while selective serotonin reuptake inhibitors (SSRIs) have been available as useful tools in the analysis of serotonergic systems, until recently no comparable noradrenaline-selective agent has been available. Our knowledge of the role of noradrenaline in depression has been gained primarily from studies using the tricyclic antidepressants (TCAs). Desipramine and nortriptyline, in particular, are the more noradrenergic of the TCAs and using these drugs, the efficacy of noradrenaline reuptake inhibition in major depression, dysthymia, long-term treatment and severe depression has been established.

However, in predicting responses to a selective noradrenaline reuptake inhibitor (selective NRI), the results obtained using TCAs as tools with which to study noradrenergic systems must be treated with caution. Although principally noradrenergic, desipramine, for example, has an affinity for other receptors in the central and peripheral nervous systems and so it is difficult to distinguish between the effects, therapeutic or non-therapeutic, that are specific to noradrenaline reuptake inhibition. Besides blocking the noradrenaline reuptake transporter, TCAs also bind, to different degrees, to muscarinic, H_1-histaminergic, α_1- and α_2-adrenoceptors, the serotonin reuptake transporter and serotonin receptors. By contrast, reboxetine, the first selective NRI, has negligible affinity for these receptors (Table 1) (Riva *et al.*, 1989; Wong *et al.*, 1997). Studies comparing desipramine with reboxetine highlighted the differences between a TCA, which is predominantly selective for noradrenaline, and a purely selective NRI.

This paper summarises the efficacy and tolerability of reboxetine and compares the clinical observations with the effects predicted by the monoamine hypothesis and the pharmacology of reboxetine.

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Table 1. Uptake and receptor data for reboxetine and comparator drugs

	K_i (nM)			K_D (nM)			
Drug	Noradrenaline	Serotonin	Noradrenaline/ serotonin	α_1	α_2	H_1	Muscarinic
Reboxetine	8	1070	0.007	10000	43000	1400	3900
Desipramine	0.9	340	0.003	130	7200	110	198
Imipramine	13	42	0.310	90	3200	11	90
Fluoxetine	280	12	23.3	5900	13000	6200	2000

K_i, inhibitor constants; K_D, equilibrium dissociation constant. Data from Richelson and Nelson (1984), Richelson and Pfenning (1984), and Wong *et al.* (1997).

Table 2. Summary of clinical trials conducted with reboxetine in patients with depression

			Number of patients		
Trial (dosage)	Duration	Patient population	Reboxetine	Placebo	Comparator
Reboxetine (10 mg/day) versus placebo	6 weeks	Hospitalised adults	28	28	–
Reboxetine (8 mg/day) versus placebo	12 months	Hospitalised and outpatient adults	143	140	–
Reboxetine (8 mg/day) versus placebo versus desipramine (200 mg/day)	4 weeks	Hospitalised adults	84	85	89
Reboxetine (8 mg/day) versus placebo versus imipramine (150–200 mg/day)	6 weeks	Outpatient adults	112	112	115
Reboxetine (8–10 mg/day) versus placebo versus fluoxetine (20–40 mg/day)	8 weeks	Outpatient adults	126	128	127
Reboxetine (8–10 mg/day) versus fluoxetine (20–40 mg/day)	8 weeks	Outpatient adults	79	–	89
Reboxetine (8–10 mg/day) versus imipramine (150–200 mg/day)	6 weeks	Hospitalised and outpatient adults	130	–	126
Reboxetine (4–6 mg/day) versus imipramine (75–100 mg/day)	8 weeks	Outpatient elderly	109	–	109

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EFFICACY OF REBOXETINE

Depression

Reboxetine has been established as an effective antidepressant in several large-scale clinical trials (Table 2). Four short-term (4–8 weeks), placebo-controlled trials were conducted in adult patients with major depressive disorder. Two trials were conducted in outpatients and two in hospitalised patients. Reboxetine (8–10 mg/day) was administered to 350 patients and placebo to 353 patients. Of these studies, three showed that reboxetine was significantly more effective than placebo in treating major depression. The fourth study showed improvements in both reboxetine- and placebo-treated patients, but although reboxetine was more effective than placebo, a strong placebo effect precluded any significant difference. Analysis of the pooled data from the four studies showed that the cumulative probability of response over the initial 4 weeks was significantly greater ($P < 0.001$) for reboxetine-treated patients. The between-treatment weighted mean difference in the decrease in mean total score on the Hamilton rating scale for depression (HAM-D; Hamilton, 1960) was 5.2 points (95% confidence interval 3.8–6.6). This compares well with the recently suggested measure of clinical relevance: an effect size difference between drug and placebo of

3–4 points on the HAM-D scale (Montgomery, 1994; 1995).

The efficacy of reboxetine is maintained during long-term treatment: a 12-month study compared reboxetine (8 mg/day) with placebo in adult patients with depression (Montgomery, 1997). At the final assessment, the percentage of patients in remission was significantly greater in the group receiving reboxetine than in the group receiving placebo (78% versus 45%, respectively, $P < 0.001$) and the relapse rate was significantly lower (22% versus 56%, respectively; $P < 0.001$).

In addition, reboxetine has been shown to be at least as effective as imipramine, desipramine and fluoxetine in the treatment of depression in short-term studies. Two studies (each lasting 6 weeks) compared reboxetine (8–10 mg/day) with imipramine (150–200 mg/day) in treating depression in hospitalised patients and outpatients (Montgomery, 1997). The response rate at the final assessment was not consistent between the two studies, but overall favoured reboxetine (between-treatment weighted mean difference 5.2%, 95% confidence interval –3.6 to 13.9%). In an 8-week study of 218 elderly outpatients with depression, while the response rate was 52% for both reboxetine (4–6 mg/day) and imipramine (75–100 mg/day), a greater proportion of patients receiving reboxetine than imipramine were judged by Clinical Global Impression-Global Improvement criteria (Guy, 1976) to be 'much to very much' improved.

In a further 4-week study (Montgomery, 1997), reboxetine (8 mg/day) was compared with desipramine (200 mg/day) in hospitalised adult patients with depression. The response rate with reboxetine, but not with desipramine, was significantly better than with placebo (60% versus 36%; $P < 0.05$) and was superior to desipramine (46%). The Clinical Global Impression-Severity of Illness scores (Guy, 1976) showed a significant advantage for reboxetine over desipramine in both the mean total score at day 28 and the percentage of patients responding to treatment.

Reboxetine (8–10 mg/day) and fluoxetine (20–40 mg/day) brought about comparable frequencies of response and improvements in HAM-D score in two 8-week trials in outpatients with major depressive disorder (Montgomery, 1997). In all, these results confirm conclusively that inhibition of noradrenaline reuptake is effective in the treatment of depression.

Severe depression

Antidepressants with significant activity on the noradrenergic system have been shown to be more effective than some SSRIs in treating severe depression. For example, mirtazapine, a noradrenergic and specific serotonergic antidepressant, is more effective than fluoxetine (Wheatley *et al.*, 1998). Venlafaxine and milnacipran, both serotonin/noradrenaline reuptake inhibitors, have proven to be superior to fluoxetine (Clerc *et al.*, 1994) and to both fluoxetine and fluvoxamine (Lopez-Ibor *et al.*, 1996), respectively. The results of clinical trials with reboxetine support this suggestion. Subset analyses of patients with severe depression have been conducted for four trials and showed reboxetine to be at least as effective as imipramine and significantly more effective than fluoxetine ($P < 0.05$) (Montgomery, 1999).

Anxiety associated with major depression

It has been established that anxiety and panic disorders have some serotonergic involvement (Stahl, 1997) and the proven efficacy of SSRIs in alleviating the symptoms is predictable from their pharmacology and serotonergic neuroanatomy. Some evidence has suggested that noradrenergic systems are also involved in these disorders (Redmond, 1979; Jann and Kurtz, 1987) although the neuroanatomical pathways are unclear. Lofepramine and desipramine, both noradrenergic antidepressants, have been shown to be effective in treating anxiety/panic disorder in placebo-controlled trials (Kalus *et al.*, 1991; Fahy *et al.*, 1992; Lydiard *et al.*, 1993). In an 8-week study comparing reboxetine (8–10 mg/day) with fluoxetine (20–40 mg/day) and placebo in patients with depression (Montgomery, 1997), items 10 and 11 on the HAM-D scale were analysed, these being the items relating to anxiety. The results showed that reboxetine is as effective as fluoxetine and significantly more effective than placebo ($P < 0.01$) in reducing anxiety associated with depression in patients with major depression.

TOLERABILITY OF NORADRENALINE REUPTAKE INHIBITION

Clinical observations

The receptor-binding profile of reboxetine predicts that the adverse side-effects associated with reboxetine should be fewer than those experienced with the TCAs and distinct from those of the SSRIs. The interaction of the TCAs with muscarinic receptors leads to dry mouth, blurred vision, constipation and urinary hesitancy. Interaction with H_1-histaminergic receptors and α_1-adrenoceptors causes sedation and hypotension. The adverse events classically associated with SSRIs include nausea, sexual dysfunction, headache, anxiety and agitation.

Clinical trials conducted with reboxetine have shown that, as expected, the adverse-event profile is different from those of the TCAs and SSRIs. Compared with desipramine, reboxetine was associated with a lower

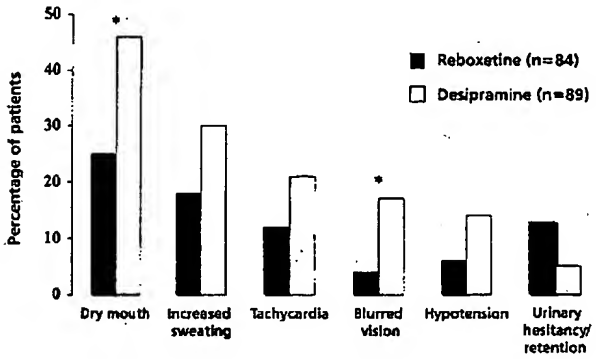

Figure 1. Frequency of adverse events in adult hospitalised patients treated with reboxetine (8 mg/day) or desipramine (200 mg/day) for 4 weeks. *$P < 0.01$. Data from Mucci, 1997.

incidence of dry mouth, increased sweating, tachycardia, blurred vision and hypotension (Fig. 1); urinary hesitancy/retention was experienced more frequently with reboxetine than with desipramine, but this did not reach statistical significance (Mucci, 1997; Ban *et al.*, 1998). Comparator trials have also shown that no adverse events were significantly more likely to occur with reboxetine than imipramine, while somnolence, tremor, hypotension and dry mouth were significantly more frequent with imipramine (Mucci, 1997). As expected, the adverse-event profiles seen in the comparison of reboxetine with fluoxetine were quite distinct from one another. Administration of fluoxetine was associated with a significantly higher risk of developing nausea, diarrhoea and somnolence, while dry mouth, constipation, hypotension, paraesthesia, urinary hesitancy/retention and flushing were significantly more likely to develop in patients receiving reboxetine (Mucci, 1997).

Elderly patients are especially sensitive to anticholinergic, cardiovascular and sedative effects. This population is at increased risk of orthostatic hypotension, which may lead to falls and fractures. A study in elderly patients with depression has shown that patients treated with reboxetine were at lower cumulative risk of developing hypotension and related symptoms than those treated with imipramine (7% versus 16%, respectively) (Montgomery, 1997). Clinically relevant decreases in standing diastolic blood pressure were less frequent in the reboxetine-treated than in the imipramine-treated patients (13% versus 22%, respectively) (Mucci, 1997).

Comparison with predictions

The profile of adverse events for a selective NRI is largely predictable from the neuroanatomy of the central nervous system, but there are some anomalies. For example, the risk of developing tremor was no greater with reboxetine than with placebo and was less than with imipramine (Mucci, 1997). This is inconsistent with the brain model, which predicts increased tremor as a noradrenergic effect caused by the activation of noradrenergic neurones in the cerebellum (Racagni, 1999). The cardiovascular effects of the TCAs are likely to be caused by their affinity for cholinergic and α_1-adrenoceptors. These interactions do not occur with reboxetine, since it has negligible affinity for the cholinergic or adrenergic receptors (Riva *et al.*, 1989; Wong *et al.*, 1997). However, given the neuroanatomy of the noradrenergic system, changes in blood pressure and heart rate would be expected with reboxetine, since central noradrenaline reuptake inhibition is likely to lead to an indirect sympathomimetic effect. It was somewhat unexpected, therefore, that in clinical trials only minimal effects on the cardiovascular system were observed with reboxetine treatment. By contrast, imipramine was associated with a significantly higher risk of developing hypotension and related symptoms and desipramine with a higher incidence of tachycardia and hypotension, compared with reboxetine (Mucci, 1997).

The incidence of urinary hesitation/retention was higher among adult patients treated with reboxetine than among those treated with placebo (5% versus 2%), desipramine (13% versus 5%) or fluoxetine (6% versus 0.5%) (Mucci, 1997). However, the need for catheterisation was rare (< 1%) (Mucci, 1997). Again, this effect is probably a result of the effects on the sympathetic nervous system. The incidence of dry mouth was lower with reboxetine than with desipramine (26% versus 45%) or imipramine (26% versus 42%). Given that reboxetine has no anticholinergic effects and has virtually no affinity for α_1-adrenoceptors, which are involved in the regulation of saliva secretion, these results are not surprising. However, the incidence was higher with reboxetine treatment than with placebo (27% versus 16%) or with fluoxetine (28% versus 7%). It has been suggested (Szabadi *et al.*, 1998) that the reduction in salivation caused by reboxetine may be caused by blockade of noradrenergic reuptake at the noradrenergic synapse on the salivary neurone, leading to noradrenergic inhibition of the parasympathetic salivary output.

Suicide

Suicide is one of the more poorly understood aspects of depression, but is a cause for great concern to the clinician when prescribing antidepressants, since these drugs potentially provide the means of committing suicide. The suicide risk in patients with depression is up to 30 times higher than in the normal population (Montgomery, 1992). There is biochemical evidence

for a correlation between serotonergic dysfunction and suicide. For example, the levels of the serotonin metabolite 5-hydroxyindoleacetic acid are low in the cerebrospinal fluid and brainstem of suicide victims, and there is evidence that the density of postsynaptic 5-HT_2 receptors is increased in the frontal cortex (Nordström and Åsberg, 1992). Clinical evidence suggests that the SSRIs are more effective than the TCAs in alleviating and protecting against the emergence of suicidal thoughts (Montgomery, 1992).

Less attention has been paid to the role of noradrenaline in suicide. Post-mortem studies of patients with depression who committed suicide have shown an increased density and affinity of the α_{2A}-adrenoceptors in the frontal cortex (Meana *et al.*, 1992; Callado *et al.*, 1998). The results of a large, placebo-controlled study of maprotiline, a highly noradrenergic antidepressant, showed that, despite showing a significant advantage over placebo in reducing the relapse rate of depression, maprotiline was associated with an increase in the number of suicide attempts (Rouillon *et al.*, 1989; Montgomery, 1992). However, a cumulative analysis of the clinical trials conducted with reboxetine, comprising over 2600 patients, found that the suicide/attempted suicide rate among those taking reboxetine (0.3%) was approximately half that of those taking fluoxetine (0.5%) or placebo (0.6%) and a third that of those taking imipramine (1.0%). This suggests a possible role for selective noradrenaline reuptake inhibition in protecting against suicidal ideation.

SUMMARY

In summary, the first available selective NRI, reboxetine, has proved to be a valuable tool in determining more precisely the role of noradrenaline in depression. Results from clinical trials using reboxetine have established the efficacy of noradrenaline reuptake inhibition in the short-term treatment of depression, reboxetine being at least as effective as imipramine, desipramine and fluoxetine. Reboxetine also maintains its therapeutic effect over long-term (12 months) administration and is effective in patients with severe depression. Although anxiety is often perceived as a serotonergic disorder, the fact that reboxetine was as effective as fluoxetine in alleviating depression-associated anxiety in patients with major depression corroborates earlier reports that desipramine and lofepramine, both noradrenergic antidepressants, are effective in anxiety/panic disorder. These results challenge current thinking on the mechanism involved.

The receptor-binding profile of reboxetine predicts a good tolerability profile and this was indeed the case in clinical trials. Patients experienced fewer anticholinergic effects with reboxetine than with the TCAs desipramine and imipramine, and less nausea and sexual dysfunction than with fluoxetine. Cardiovascular side-effects were minimal. Since reboxetine is highly selective for the noradrenaline reuptake transporter, side-effects are likely to be caused, not by interaction with cholinergic, histamine, serotonin or adrenergic receptors, but by central noradrenaline reuptake inhibition. The differences between reboxetine and desipramine are of particular interest because, until now, desipramine has been the most noradrenergic antidepressant to be used and much of our current perception of the role of noradrenaline is derived from observations of its effects.

In conclusion, reboxetine, the first selective NRI, has been shown to be an effective and well-tolerated antidepressant therapy in all grades of major depression. Clinical experience with reboxetine challenges our existing perception of the role of noradrenaline in depression and other affective disorders, which has previously been based on our experience of noradrenergic TCAs.

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